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10/519,539	03/15/2005	Karin Butz	085449-0158	3633

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,539	BUTZ ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-57* is/are pending in the application.

4a) Of the above claim(s) *25-31,33,42-53 and 55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,32,34-41 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed June 20, 2006 in response to the Office Action of May 19, 2006 is acknowledged. Applicant elected with traverse Group I, claims 22-24, 32, 34-41, and 54, SEQ ID NO:127, and the species "melanoma cells" and the active agent "intercalating agents".

2. Applicants argue that the examination of at least Groups I, II, and V is not unduly burdensome. Group II is directed to nucleic acids (corresponding to the peptides of Group I) and Group V is directed to a method of sensitizing a cell for apoptosis using such nucleic acids (p. 3).

The argument has been considered but is not found persuasive. Although the nucleic acids of Group II encode the peptides of Group I, they do not share the same special technical feature because they are chemically, structurally and functionally distinct. Furthermore, searching the inventions of Groups I and II together would impose a serious search burden. In the instant case, the search of the polypeptides and polynucleotides are not coextensive. In cases such as this one where descriptive sequence information is provided, the sequences are searched in appropriate database. There is search burden also in the non-patent literature. Prior to the concomitant isolation and expression of the sequences of interest there may be journal articles devoted solely to polypeptides which would not have described the polynucleotide. Similarly, there may have been "classical" genetics papers which had no knowledge of the polypeptide but spoke to the gene. Searching, therefore is not coextensive. This

search requires an extensive analysis of the art retrieved in a sequence search and will require an in-depth analysis of technical literature. The scope of polynucleotides as claimed extend beyond the polynucleotide that encodes the claimed polypeptides as explained above, furthermore, a search of the nucleic acid molecules of Group I would require an oligonucleotide search, which is not likely to result in relevant art with respect to the polypeptide of Group II. As such, it would be burdensome to search the inventions of Groups I and II. A search of Group V as drawn to a method using the polynucleotides of Group II would not be coextensive with searching a method using the polypeptides of Group I because the methods require using chemically, structurally and functionally distinct agents that do not share a special technical feature. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application is considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d). Group I is the main invention. After that, all other products and methods are broken out as separate groups (see 37 CFR 1.475(d).).

3. Applicants traverse the restriction to a single peptide on the grounds that the MPEP provides a reasonable number of sequences (e.g., up to 10) can be searches in one application.

This argument has been considered but is not found persuasive because the peptide sequences do not share significant structural and functional similarities, hence do not share the same special technical feature. Each peptide of the instant application

is considered an independent and distinct invention. The MPEP 803.04 states, with regards to searching polynucleotide or peptide sequences, (which Applicants appear to be referring to):

"Polynucleotide molecules defined by their nucleic acid sequence (hereinafter "nucleotide sequences") that encode different proteins are structurally distinct chemical compounds. **These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq.** Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Director has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See Examination of Patent Applications Containing Nucleotide Sequences, 1192 O.G. 68 **(November 19, 1996).**

It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patentably indistinct from the selected sequences will also be examined.

Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.
In some exceptional cases, the complex nature of the claimed material, **for example a protein amino acid sequence reciting three dimensional folds, may necessitate that the reasonable number of sequences to be selected be less than ten**. In other cases, applicants may petition pursuant to 37 CFR 1.181 for examination of additional nucleotide sequences by providing evidence that the different nucleotide sequences do not cover independent and distinct inventions."

Examiner points out that the Director partially waived requirements of 37 CFR 1.141 et seq. to "permit a reasonable number of such nucleotide sequences to be claimed in a single application" **in 1996.** The size of the sequence and literature database required to search a single sequence has exponentially increased every year for **10 years** since the Director's statement. A search for more than one amino acid sequence would not necessarily result in or overlap the search of another sequence and the current size of the sequence database clearly creates undue burden on the Office. For these reasons, the restriction requirement is deemed to be proper and is therefore made FINAL.

4. Claims 22-57 are pending. Claims 25-31, 33, 42-53, and 55-57 are withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 22-24, 32, 34-41, and 54 are currently under prosecution.

Specification

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2). Specifically, there is no SEQ ID NO identified with the sequence disclosed **on page 4, line 9 (AEIYES).** Applicant is required to provide (1) a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, (2) a substitute paper copy of the "Sequence Listing", (3) an amendment directing the entry of that paper into the specification, and (4) a statement that the content of the paper and computer readable copies are the same, and, where applicable, include no new matter, as required by CFR 1.821(d) which requires a reference to a particular sequence identifier (i.e., SEQ DI NO:#) be made in the specification and claims wherever a reference is made to that sequence (See MPEP 2422.04).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of

the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of Ex parte Steigewald, 131 USPQ 74 (Bd. App. 1961); Ex parte Hall, 83 USPQ 38 (Bd.App. 1948); and Ex parte Hasche, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 54 recites the broad recitation IAPs, and the claim also recites "preferably livin-β" which is the narrower statement of the range/limitation.

7. Claims 32, and 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the binding of the peptide to the IAP or livin-β, and a correlation step back to the preamble such as "wherein the cell is sensitized for apoptosis". Claim 32 recites the use of at least one peptide but it does not recite how it is used. Claim 34 recites that the sensitization for apoptosis occurs by binding of IAPs but does not recite what binds to the IAPs.

8. Claims 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Claim 23 recites "wherein the peptide is linked to a second moiety which mediates the uptake into a cell". It is grammatically unclear exactly what is being taken into the cell. The uptake of what? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 22-24, 32, 34-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to a peptide, a **fragment or derivative thereof**, which sensitizes cells for apoptosis comprising SEQ ID NO:127 (claim 22), wherein the peptide is linked to a **second moiety** which mediates the uptake into a cell (claim 23), wherein the second moiety is a **carrier** (claim 24), a method of sensitizing a cell for apoptosis by using at least one peptide of claim 22, optionally in combination with at least one **active compound** (claim 32-38), a medicament for the treatment of cancer comprising a peptide of claim 22 and a pharmaceutically acceptable carrier, optionally in combination with an **active compound** (claim 39), wherein the active compound is

intercalating agents (claim 41), a diagnostic kit for the detection of IAPs in cancer cells comprising at least one peptide as defined in claim 22 (claim 54).

The specification discloses SEQ ID NO:127 as peptide number 41 in Table 2 or peptide number 75 according to inventors numbering system (p. 4, lines 3-5). SEQ ID NO:127 specifically binds the IAP livin-β (Table 3). The specification discloses that a derivative or fragment peptide has one or more amino acids substituted by one or more amino acids different from the original one(s), or peptides the amino acid sequence of which is either extended, shortened, or both, on either the aminoterminal, or the carboxyterminal or both ends with respect to the original proteins, provided that the binding properties of the peptides remain unaffected (p. 3, lines 11-20). The specification discloses a second moiety or carrier that enables the penetration of the peptides through the cell membrane into the cell and lists non-limiting examples such as TAT, poly-arginine, Antennapedia (p. 5, lines 25-30 to p. 6, lines 1-16). The specification discloses an "active compound as a compound other than the peptide, fragment or derivative thereof, which is able to induce apoptosis or which inhibits cell proliferation. The specification discloses that one class of active compounds are chemical compounds having a cytostatic or antineoplastic effect ("cytostatic compound") and discloses a list of compounds including intercalating agents such as adriamycin (doxorubicin) or mitoxantrone (p. 9, lines 27-30 to p. 27). The specification discloses another class of active compounds which are able to sensitize for or induce apoptosis by binding death receptors (death receptor agonists) (p. 10, lines 29-35 to p. 11, lines 1-6). The specification does not disclose any other fragments or derivatives of SEQ ID

NO:127, second moieties which mediate the uptake into a cell, carriers, or active compounds as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of "a peptide, a fragment or derivative thereof" "second moiety which mediates the uptake into a cell", "carrier", and "active compound". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because

> it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed

correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of fragments or derivatives of SEQ ID NO:127, second moieties which mediate the uptake into a cell, carriers, or active compounds, per Lilly by structurally describing representative fragments or derivatives of SEQ ID NO:127, second moieties which mediate the uptake into a cell, carriers, or active compounds or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe fragments or derivatives of SEQ ID NO:127, second moieties which mediate the uptake into a cell, carriers, or active compounds useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses SEQ ID NO:127, specific

cell permeation sequences such as TAT and poly-arginine, and intercalating agents doxorubicin or mitoxantrone, this does not provide a description of the broadly claimed fragments or derivatives of SEQ ID NO:127, second moieties which mediate the uptake into a cell, carriers, or active compounds that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe fragments or derivatives of SEQ ID NO:127, second moieties which mediate the uptake into a cell, carriers, or active compounds by the test set out in Lilly because the specification describes only SEQ ID NO:127, specific cell permeation sequences such as TAT and poly-arginine, and intercalating agents doxorubicin or mitoxantrone. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of fragments or derivatives of SEQ ID NO:127, second moieties which mediate the uptake into a cell, carriers, or active compounds that is required to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed method of sensitizing a cell of apoptosis uses, it also fails to adequately describe the method.

10. Claims 32, and 34-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **an *in vitro* method of sensitizing a cell for apoptosis by administering a peptide consisting of SEQ ID NO:127 operatively**

attached to a sequence that internalizes said peptide, wherein the cell has livin-β-inhibited apoptosis, and wherein said peptide binds to livin-β, does not reasonably provide enablement for a method of sensitizing a cell for apoptosis by using at least one peptide of claim 22, optionally in combination with at least one active compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of sensitizing a cell for apoptosis by using at least one peptide of claim 22, optionally in combination with at least one active compound (claim 32), wherein the sensitization for apoptosis occurs by binding of IAPs (claim 34), wherein the IAP is livin-β (claim 35), wherein the cell which is sensitized for apoptosis is a cancer cell (claim 37), wherein the cancer cell is melanoma (claim 37), wherein the cancer is melanoma (claim 38).

The specification discloses SEQ ID NO:127 as peptide number 41 in Table 2 or peptide number 75 according to inventors numbering system (p. 4, lines 3-5). SEQ ID NO:127 specifically binds the IAP livin-β and not to any other IAPs tested (Table 3). Example 4 of the specification discloses that HeLa and melanoma cells transfected with SEQ ID NO:127 blocked the growth of the cells which were livin-β positive, and did not affect the growth of livin-β negative cells (p. 18). Example 5 of the specification discloses fusing SEQ ID NO:127 to poly-arginine R9 (an internalization sequence), and administering the fusion complex to HeLa cells. Ectopic expression of the peptide led to a sensitization of livin-positive cells for pro-apoptotic drugs such as doxorubicin. Administration of doxorubicin resulted in an increased concentration of active caspase (Fig. 4) and the increased caspase-3 activity directly correlated with an increased cleavage of the caspase-3 substrate PARP and an increase of apoptosis of HeLa cells (p. 18).

The claims are broadly drawn to a method of sensitizing cells for apoptosis both ***in vivo*** and *in vitro*, using **any peptide fragments and derivatives** of unknown

sequences, using **any cells** that may not express livin-β or have livin-β inhibited apoptosis, and using a **second moiety** that is not required to internalize the peptide.

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for sensitizing a cell for apoptosis using any derivative or fragment of SEQ ID NO:127, using any second moiety that mediates uptake into the cell, using any carrier, and in any cell regardless of livin-β expression. The specification discloses that SEQ ID NO:127 binds "in a highly specific manner" to livin-β in Table 3, and not to any other tested IAPs (p. 17, line 31). The specification discloses that peptide SEQ ID NO:127 was fused to poly-arginine R9, a sequence that internalized the peptide and enabled the peptide to bind to livin-β (Example 5). SEQ ID NO:127 could not affect the growth or apoptosis of cells that were livin-β negative (Examples 4 and 5), hence one of skill in the art could not predictably sensitize cells for apoptosis unless the cells express livin-β and SEQ ID NO:127 is internalized to bind livin-β.

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for sensitizing a cell for apoptosis *in vivo*. The specification only discloses an *in vitro* example of internalizing SEQ ID NO:127 into livin-β expressing HeLa cells and correlation to increased caspase-3 activity and apoptosis after administration of doxorubicin. Those of skill in them art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally

lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells

in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Given the teaching of the art, one of skill in the art could not predictably sensitize a cell *in vivo* for apoptosis by using SEQ ID NO:127.

Therefore, in view of the state of the art, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

11. Claims 39-41 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not

'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a medicament for the treatment of cancer comprising a peptide of claim 22 and a pharmaceutically acceptable carrier, optionally in combination with an active compound (claim 39), wherein the cancer is melanoma (claim 40), wherein the active compound is intercalating agents (claim 41), and a diagnostic kit for the detection of IAPs, preferably livin-β, in cancer cells comprising at least one peptide as defined in claim 22 (claim 54).

The specification discloses SEQ ID NO:127 as peptide number 41 in Table 2 or peptide number 75 according to inventors numbering system (p. 4, lines 3-5). SEQ ID NO:127 specifically binds the IAP livin-β and not to any other IAPs tested (Table 3). Example 4 of the specification discloses that HeLa and melanoma cells transfected with SEQ ID NO:127 blocked the growth of the cells which were livin-β positive, and did not affect the growth of livin-β negative cells (p. 18). Example 5 of the specification

discloses fusing SEQ ID NO:127 to poly-arginine R9 (an internalization sequence), and administering the fusion complex to HeLa cells. Ectopic expression of the peptide led to a sensitization of livin-positive cells for pro-apoptotic drugs such as doxorubicin. Administration of doxorubicin resulted in an increased concentration of active caspase (Fig. 4) and the increased caspase-3 activity directly correlated with an increased cleavage of the caspase-3 substrate PARP and an increase of apoptosis of HeLa cells (p. 18).

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for treating cancer using SEQ ID NO:127 or fragments or derivatives thereof. The specification discloses sensitization of HeLa cells to apoptosis upon administration of SEQ ID NO:127 fused to poly-arginine R9 and administration of doxorubicin (Example 5). However, the specification does not provide guidance or examples for treating cancer *in vivo*. Those of skill in them art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic

characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and

NO:127 would not predictably function to treat cancer as inferred by the claim and contemplated by the specification.

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for using SEQ ID NO:127 as a diagnostic. The specification contemplates using SEQ ID NO:127 to detect IAPs in tumor cells that fail to undergo apoptosis (p. 13, lines 25-31) and discloses that SEQ ID NO:127 binds livin-β, one IAP, in a highly specific manner (Table 3). While it is clear from the specification that SEQ ID NO:127 specifically binds to livin-β and could detect livin-β, the specification provides no guidance or examples for diagnosing tumor cells that fail to undergo apoptosis by detecting IAPs. The specification has not provided a nexus between the **detection** of IAPs using SEQ ID NO:127 and the **diagnosis** of any condition in cancer cells either *in vivo* or *in vitro*, hence one of skill in the art could not predictably use SEQ ID NO:127 as a diagnostic.

Therefore, in view of the state of the art, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

12. **Conclusion:** No claim is allowed. Claims 22-24, 32, 34-41 are rejected under 35 U.S.C. 112, first paragraph, but appear to be free of the prior art. The closes prior art appears to be Du et al (Cell, 2000, 102:33-42). Du et al teach "Smac", a mitochondrial protein that binds to IAPs and sensitizes cell for apoptosis. Du et al do not teach or suggest a peptide that comprises SEQ ID NO:127.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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